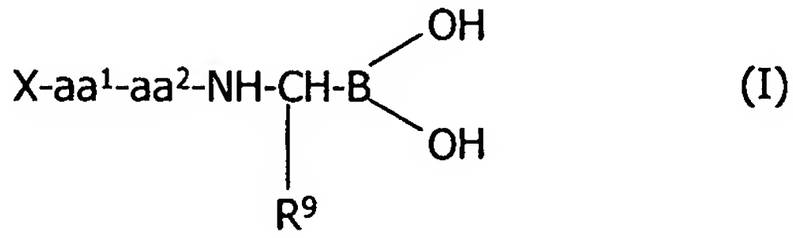
Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

Claim 1 (currently amended): A compound selected from boronic acids of formula (I), and pharmaceutically acceptable salts, prodrugs and pharmaceutically acceptable prodrug salts thereof:



(I)

wherein

X is H (to form NH_2) or an amino-protecting group;

aa^1 is an amino acid residue having a side chain selected from formula (A) and (B):

$$-(CO)_a-(CH_2)_b-D_c-(CH_2)_d-E \qquad (A)$$

$$-(CO)_a-(CH_2)_b-D_c-C_e(E^1)(E^2)(E^3) \qquad (B)$$

wherein

a is 0 or 1;

e is 1;

b and d are independently 0 or an integer such that (b+d) is from 0 to 5 or, as the case may be, (b+e) is from 1 to 5;

c is 0 or 1;

D is O or S;

E is a saturated or unsaturated cyclic hydrocarbyl group ~~which normally contains up to 14 members~~; and

E^1, E^2 and E^3 are each independently selected from the group consisting of 5-6 membered saturated or unsaturated hydrocarbyl rings, or one of E^1, E^2 and E^3 is hydrogen and the other two are a said hydrocarbyl ring,

and wherein E, E^1, E^2 and E^3 are halogenated;

aa^2 is a residue of an amino acid which binds to the thrombin S2 subsite; and

R^9 is a straight chain alkyl group interrupted by one or more ether linkages and in which the total number of oxygen and carbon atoms is 3, 4, 5 or 6 or R^9 is $-(CH_2)_m$-W where m is from 2, 3, 4 or 5 and W is –OH or halogen.

Claim 2 (original): A compound of claim 1 wherein R^9 is an alkoxyalkyl group.

Claim 3 (currently amended): A compound of claim 1 ~~or claim 2~~ wherein E, E^1, E^2 and E^3 are each independently selected from the group consisting of halogenated 6-membered rings.

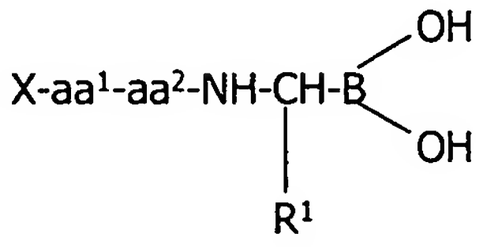
Claim 4 (currently amended): A compound of ~~any of claims 1 to 3~~ claim 1 wherein a and c are both 0 and (a+b+c+d) and (a+b+c+e) are 1, 2 or 3~~, particularly 1~~.

Claim 5 (original): A compound of claim 4 wherein aa^1 is of (R)-configuration, aa^2 is of (S)-configuration, and the fragment $-NHCH(R^9)$-B(OH) is of (R)-configuration.

Claim 6 (canceled)

Claim 7 (currently amended): A compound of ~~any of claims 1 to 6~~ claim 1 wherein E, E^1, E^2 and E^3 are fluorinated.

Claim 8 (currently amended): A compound selected from boronic acids of formula (II), and pharmaceutically acceptable salts, prodrugs and prodrug salts thereof:



(II)

where:

X is H (to form NH_2) or an amino-protecting group;

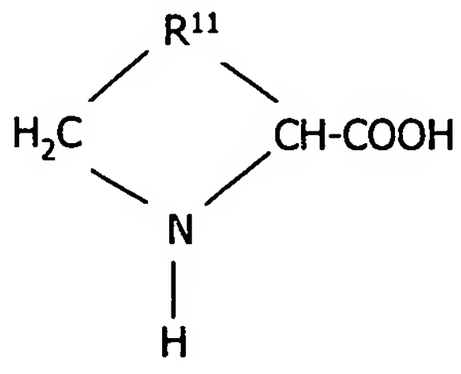
aa^1 is an amino acid having a side chain which is C_1-C_5 alkyl substituted by one or two moieties selected from fluorophenyl, cyclohexyl and fluorocyclohexyl;

aa^2 is an imino acid having from 4 to 6 ring members;

R^1 is a group of the formula $-(CH_2)_S-Z$, where s is 2, 3 or 4 and Z is –OH, –OMe, –OEt or halogen ~~(F, Cl, Br or I)~~.

Claim 9 (currently amended): A compound of claim 8 ~~to claim 9~~ wherein aa^1 is selected from 4-F-Phe, 4-F-Dpa, 4-F-Dcha and 4-F-Cha.

Claim 10 (currently amended): A compound of claim 8 wherein aa^2 is a residue of an imino acid of formula (IV)



(IV)

where R^{11} is -CH_2-, -CH_2-CH_2-, -CH=CH-, -S-CH_2-, -S-$C(CH_3)_2$- or –CH_2-CH_2-CH_2-, which group, when the ring is 5- or 6- membered, is optionally substituted at one or more -CH_2- groups by from 1 to 3 C_1-C_3 alkyl groups, and optionally aa^2 is an (S)-proline residue~~, e.g. aa^1-aa^2 is (R) Phe (S) Pro~~.

Claim 11 (currently amended): A compound of ~~any of claims 8 to 10~~ claim 8 wherein aa^1 is of (R)-configuration and/or aa^2 is of (S)-configuration and/or the fragment -NH-CH(R^1)-$B(OH)_2$ is of (R)-configuration.

Claim 12 (currently amended): A compound of ~~any of claims8 to 12~~ claim 8 wherein R^1 is 2-bromoethyl, 2-chloroethyl, 2-methoxyethyl, 3-bromopropyl, 3-chloropropyl or 3-methoxypropyl~~, e.g. is 3 methoxypropyl~~.

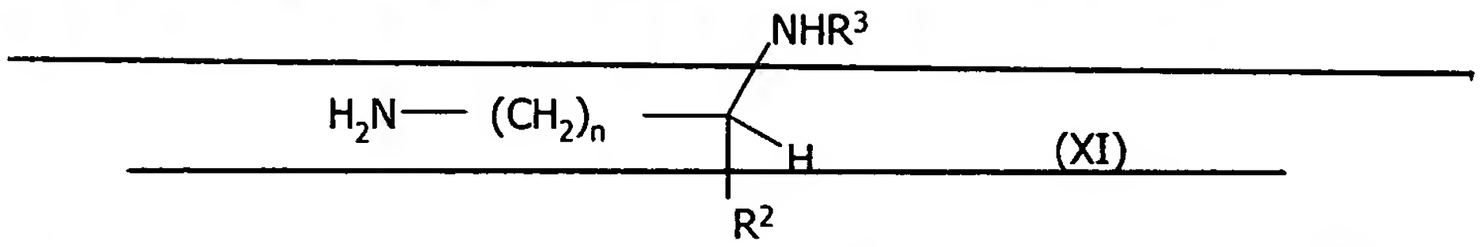
Claim 13 (currently amended): A compound of ~~any of claims 8 to 13~~ claim 8 where X is R^6-$(CH_2)_p$-C(O)-, R^6-$(CH_2)_p$-$S(O)_2$-, R^6-$(CH_2)_p$-NH-C(O)- or R^6-$(CH_2)_p$-O-C(O)- wherein p is 0, 1, 2, 3, 4, 5 or 6 and R^6 is H or a 5 to 13-membered cyclic group optionally substituted by one or more ~~(e.g. 1, 2, 3, 4 or 5)~~ halogens ~~(e.g. F), for example at least at the 4 position~~, and/or by 1, 2 or 3 substituents selected from amino, nitro, hydroxy, a C_5-C_6 cyclic group, C_1-C_4 alkyl and C_1-C_4 alkyl containing, and/or linked to the cyclic group through, an in-chain O, the aforesaid alkyl groups optionally being substituted by a substituent selected from halogen, amino, nitro, hydroxy and a C_5-C_6 cyclic group~~, and optionally said 5 to 13 membered cyclic group is aromatic or heteroaromatic, e.g. is phenyl or a 6 membered heteroaromatic group, for example X is benzyloxycarbonyl~~.

Claim 14 (currently amended): A compound of claim 8 ~~or claim 13~~ wherein the boronic acid is of formula (VIII):

X-(R)-4-F-Phe-(S)-Pro-Mpg-$B(OH)_2$ (VIII).

Claim 15 (currently amended): A compound of ~~any preceding claim~~ claim 1 which is in the form of a base addition salt of the boronic acid.

Claim 16 (currently amended): A compound of claim 15 which comprises a salt of the peptide boronic acid with an alkali metal or a strongly basic organic nitrogen-containing compound~~, and optionally wherein the strongly basic organic nitrogen-containing compound is a guanidine, a guanidine analogue or an amine, e.g. comprises a salt of the boronic acid with an alkali metal, an aminosugar, a guanidine, an amine of formula (XI):~~



~~where n is from 1 to 6, R^2 is H, carboxylate or derivatised carboxylate, R^3 is H, C_1-C_4 alkyl or a residue of a natural or unnatural amino acid, e.g. a salt with lysine, arginine or a glucamine~~.

Claim 17 (original): A compound of claim 15 which comprises a salt of the boronic acid with a metal.

Claim 18 (currently amended): A compound of claim 17 wherein the metal comprises an alkali metal salt~~, e.g. sodium or lithium~~.

Claim 19 (currently amended): A compound of ~~any of claims 15 to 18~~ claim 15 which comprises boronate ions derived from the peptide boronic acid and has a stoichiometry consistent with the boronate ions carrying a single negative charge.

Claim 20 (currently amended): A pharmaceutical formulation comprising a compound of ~~any of claims 1 to 19~~ claim 1.

Claim 21 (currently amended): A pharmaceutical formulation of claim 20 which is adapted for intravenous administration or for subcutaneous administration~~, e.g. comprises the compound in the form of a finely divided solid for reconstitution as a solution ready for administration~~.

Claim 22 (currently amended): A pharmaceutical formulation of claim 20 which is adapted for oral administration~~, e.g. is a tablet capsule or is a particulate formulation in a sachet~~.

Claims 23-24 (cancelled)

Claim 25 (original): A medicament comprising a salt, sugar ester or other soluble derivative of a boronic acid which is a selective thrombin inhibitor and has a neutral aminoboronic acid residue capable of binding to the thrombin S1 subsite linked to a hydrophobic moiety capable of binding to the thrombin S2 and S3 subsites, the hydrophobic moiety comprising a fluorinated ring in its S3-binding part and the salt comprising a cation having a valency n and having an observed stoichiometry consistent with a notional stoichiometry (boronic acid:cation) of n:1.

Claim 26 (currently amended): A method for making a product, comprising: contacting a boronic acid as defined in ~~any of claims 1 to 14~~ <u>claim 1</u> with a pharmaceutically acceptable base to form the product.

Claim 27 (original): The method of claim 26 which further comprises formulating the product into a pharmaceutical formulation.

Claim 28 (new): A method of inhibiting thrombin in the treatment of a disease, comprising administering to a mammal an effective amount of a compound of claim 1.